PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PV/398/PCT	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/CZ 03/00056	International filing date *(day/month/year)* 21.10.2003	Priority date *(day/month/year)* 25.10.2002
International Patent Classification (IPC) or both national classification and IPC A61K31/4406		
Applicant LECIVA, A.S.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
09.04.2004	03.03.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Elliott, A Telephone No. +49 89 2399-8218

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CZ 03/00056

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1, 2, 4-11	as originally filed
3, 3a	received on 19.01.2005 with letter of 13.01.2005

Claims, Numbers

8 (part), 9-16	as originally filed
1-7, 8 (part)	received on 19.01.2005 with letter of 13.01.2005

Drawings, Sheets

1/8-8/8	received on 30.10.2003 with letter of 30.10.2003

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-16
	No:	Claims	-
Inventive step (IS)	Yes:	Claims	1-16
	No:	Claims	-
Industrial applicability (IA)	Yes:	Claims	1-16
	No:	Claims	-

2. Citations and explanations

   see separate sheet

The application relates to crystalline, hydrated forms of risedronic acid wherein the sodium and water contents lie within particular limits with respect to each other.

The following documents have been taken into account:

D1: WO 03/086355 A (TEVA PHARMACEUTICAL INDUSTRIES LTD) 23 October 2003 (2003-10-23)
D2: US-A-2003195170
D3: GOSSMAN W L ET AL: "Three hydrates of the bisphonate risedronate, consisting of one molecular and two ionic structures" ACTA CRYSTALLOGRAPHICA SECTION C, vol. c59, 11 January 2003 (2003-01-11), pages m33-m36, XP009024776 ISSN: 0108-2701
D4: WO 01/56983 A (PROCTER & GAMBLE) 9 August 2001 (2001-08-09)
D5: KUSHIDA K: "Sodium risedronate hydrate" RINSHO TO YAKUBUTSU CHIRYO, vol. 21, no. 10, 2002, pages 1040-1, XP001157194 ISSN: 0913-7505
D6: REDMAN-FUREY N L ET AL: "Thermoanalytical characterisation of the hydration states of risedronate" PROCEEDINGS OF THE NATAS ANNUAL CONFERENCE ON THERMAL ANALYSIS AND APPLICATIONS, no. 30th, 21 - 22 September 2002, pages 733-8, XP009024613

Re Item VIII.

A discrepancy was discovered is the way in which the weight percent of sodium and crystalline water was calculated. If, as originally filed, the calculations are done based in the anhydrous substance, the compounds of claims 2 and 3 as originally filed, if pure, would fall outside the ranges given for sodium and water content. If, on the other hand, these weight percentages were to be with respect to the weight of the whole molecule, the compound of claims 2 and 3 falls within the given ranges. Hence amendments to the claims and the corresponding part of the description are considered to be allowable as the correction of an obvious error.

Re Item V.

The prior art discloses a number of hydrated forms of sodium risedronate:

D4 - the hemipentahydrate and monohydrate of risedronate sodium.

D5 - again the hemipentahydrate of risedronate sodium.

D6 - again the hemipentahydrate and monohydrate of risedronate sodium

The monohydrate and hemipentahydrate of risedronate sodium have the following sodium and water of crystallisation contents:

	%Na based on the anhydrous substance	%Na based on the whole molecule	%H2O
monohydrate	7.54%	7.1%	5.58%
hemipentahydrate	7.54%	6.57%	12.86%

The weight percentages are outside the ranges stated in modified claim 1. Claims 1-11 are therefore novel. Claims 12 to 15 directed to a method of preparing the novel hydrated forms of claims 1-11 are therefore also to be regarded as novel as is the pharmaceutical composition of claim 16.

As regards inventive step, the method of preparing the monohydrate and hemipentahydrate forms of risedronate sodium in D4 would appear very similar if not the same as that of claims 12-15. However, D4 also indicates that the product is a mixture of the hemipentahydrate and the monohydrate so that the skilled person has no incentive from D4 to use D4's method to prepare other hydrated forms of risedronate sodium. An inventive step is therefore acknowledged for all claims.

Re Item VI.

D1, published after the present application's filing date is not to be considered prior art under Rule 64.3 PCT. This document addresses polymorphs of risedronate sodium and only mentions the hemipentahydrate as a hydrated form.

D2, published in the present application's priority interval ,is also not to be considered as prior art under Rule 64.3 PCT. D2's disclosure is the same as D1's.

D3, again published in the present application's priority interval ,is also not to be considered as prior art under Rule 64.3 PCT. D3 discloses the dihydrate and hemipentahydrate of risedronate sodium.

Re Item VII.

The dependency of claim 14 is incorrect.